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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,678	03/25/2004	Jeremy Green	VPI/02-137 US	6199

27916 7590 12/27/2007
VERTEX PHARMACEUTICALS INC.
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CAMBRIDGE, MA 02139-4242

EXAMINER

CHANDRAKUMAR, NIZAL S

ART UNIT	PAPER NUMBER
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1625

MAIL DATE	DELIVERY MODE
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12/27/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/808,678	Applicant(s) GREEN ET AL.	
	Examiner Nizal S. Chandrakumar	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/09/2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 47,50,52,53,59-68 and 71-101 is/are pending in the application.
- 4a) Of the above claim(s) 52 and 53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 47,50,59-68 and 71-101 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants response filed 10/09/2007 is acknowledged.

The finality of the previously presented office action filed 08/06/2007 is withdrawn.

Claims 47, 50, 52-53, 59-68, 71-101 are pending.

Election/Restrictions

During a telephone conversation with Daniel A. Pearson 617-444-6790 on 12/11/2007 and on 12/12/2007 the Applicant agreed for the following grouping of the claims:

Group I, Claims 47, 59-68 and 71-101 claims drawn to composition containing compounds of formula I and claim 50 drawn to method of inhibiting c-Met kinase using compound of formula I.

Group, II, Claims 52 and 53 drawn to method of treating diseases using the compounds of formula I.

During the above-mentioned Telephone conversation, Mr. Daniel A. Pearson also agreed for the following amendments to the claims.

DELETE claim 49

DELETE claim 47, line 1, "an effective amount of"

Applicant's election of Group I in the above-mentioned telephone conversation is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Affirmation of this election must be made by applicant in replying to this Office action. Claims 52 and 53 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

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Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

At the point when claims 47, 50, 59-68, 71-101 are found allowable, method claims 52 and 53 will be rejoined under the provision of MPEP 821.04.

Response to Applicants Remarks filed 10/09/2007:

Applicant's response is not addressed at this point because of the new Election/Restrictions and because of the above-mentioned amendment to the base claim 47.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47, 59-68 and 71-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims are drawn to substituents that are not adequately defined. Claims are drawn to variables such as Ar1 and Cy1 as 5-7 and 3-7 membered ring systems without distinctly claiming what ring systems the applicant is seeking protection for.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 50, 59-68 and 71-100 as well as claim 101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of compounds of the formula I, does not reasonably provide enablement for the plurality of possible structures claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification is enabling for making a limited number of possibilities for the R1, R2, R3 and R4 variables. The specification is enabling for T = A1 = CH. It is not seen, for example, where in the specification, enablement is present for R2 being other than H. In addition, the claims are drawn to many functionalities for the linker L variable that are not compatible with the direction and working examples provided for making the claimed inventions.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: The claims are drawn to compounds with many independently varying substitutions layered on top of substitutions rendering the number of conceivable structures large. Further

the claims are drawn to compounds with undefined carbocyclic and heterocyclic rings of unknown connectivity mode, making the number of conceivable structures indefinite.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic and medicinal chemistry, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction provided by the inventor and the presence or absence of working examples: The specification contains many examples pertaining to compounds wherein Ar1 and or Cy1 are a substituted phenyl group.

There is no example of compounds of formula I wherein R2 is other than H.

There is no example of compounds of formula I wherein T is other than CH.

There is no example of compounds of formula I wherein A3 is other than CH.

There is no example wherein Cy1 is partially unsaturated monocyclic with 0-3 heteroatoms.

There is no direction or working examples provided in the specification for making compounds wherein the m is other than 0. In addition, the direction provided in the specification on page 43 and 44 are not extendable for making compound of formula I wherein m is 0 and L is S. There is no working example or guidance for making such compounds. It is unclear where in the specification the chemistry for making compound I-10 is disclosed.

Many of the variables claimed for the linker L ^{are} incompatible with the direction and guidance provided in the specification on page 43-44. For example, the thio-carbonyl forming reaction step would be severely compromised if L (or Z or ZRX is $-\text{C}(\text{O})\text{C}(\text{O})-$). Variables such as $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})-$ would not only interfere with first step used in the introduction of Ar1/Cy12 moiety but are also incompatible with the last step, namely hydroxylamine reaction. The specification is silent with regards to the functional group transformations needed to make non-enabled variants, for example after the introduction of the hydroxylamine function.

The specification does not provide citations (commercial or literature) for procuring the starting materials usable that could substitute for the lack of working examples with respect to non-enabled substitutions. For instance, it is not seen where the specification discloses methods for making or procuring, at least, conceivable starting materials needed for the above-mentioned partially unsaturated Cy1 variables or any of CY1 variables indicated in claim 64.

The specification contains description of biological assays and generic statements with regards to the activity compounds. There is nothing in the disclosure regarding minimum structure required for inhibiting C-Met kinase activity. As such, for example with regards to claim 50, it is unclear what specific embodiment of all the structures claimed would have the ability to inhibit kinase activity.

The state and the predictability of the art: With regards to making of the compounds, in spite of major advances in protecting group strategies in synthesis, the state of the art is unpredictable as to functional group compatibility during many chemical transformations. The existence of such unpredictabilities and uncertainties would prevent one of ordinary skill in the art from accepting any process such as the ones presented in the working examples on its face as universally applicable for all the substitutions claimed. Further the medicinal chemistry art is unpredictable with regards to activity of a given compound.

The quantity of experimentation: For the reasons presented above, in order to utilize the invention as claimed, that is to make and use the claimed compounds with all the variables, the skilled artisan would be presented with an unpredictable amount of experimentation. The instant disclosure is broad and generic. Further, based on the disclosure (generic statements) with respect to the biological activity of the compounds of the formula I, it is not clear what specific embodiments would be required in order for one of ordinary skill in the art at the time the invention was made to make and use the compounds of the formula I commensurate with the full scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

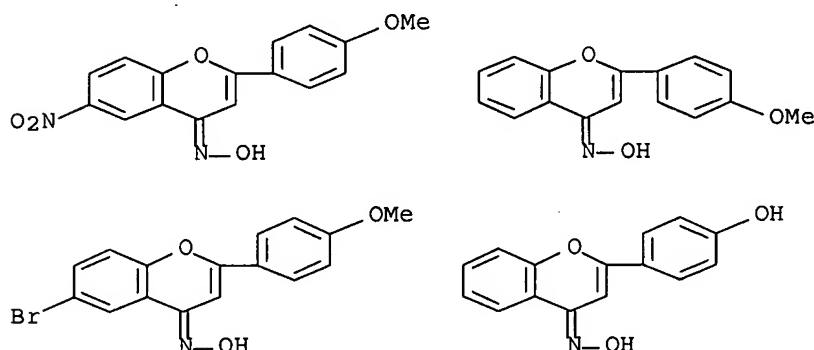
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 47, 59 and 63 are rejected under 35 U.S.C. 102(b) as being anticipated in the prior art.

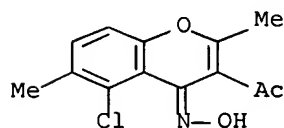
Examples of prior art references:

Ishchenko et al. (Geterotsiklicheskikh Soedinenii) (2002), 38(3), 274-280) teach,



corresponding to compounds of formula 1. The first compound corresponds to formula 1 wherein m is 0, Ar1 is substituted 6-membered ring, Z is bond; Rx is OR', R' being C1 aliphatic group; R2 is H, R3 is H, A1=A3=CH (i.e., R4 is H); A2 = CR4, R4 being NO2.

Lacova et al. (Molecules [Electronic Publication] (1998), 3(3), 120-131)

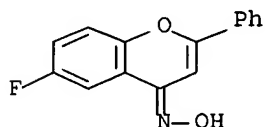


corresponding to compound of formula I wherein R1 is methyl (m is 0, R is C1 aliphatic group); R2 is

C(O)R, R being C1 aliphatic group; R3=halogen; A1 = CR4 of which R4 is (L)mR in which m is 0 and R is C1 aliphatic group; A2 is CR4 of which R4 is H;;A3 is CR4 of which R4 is halogen.

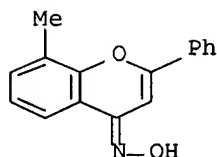
Claim 101 is rejected under 35 U.S.C. 102(b) as being anticipated by Meshcheryakova et al. (Khimiko-Farmatsevticheskii Zhurnal (1976), 10(3), 37-41).

Meshcheryakova et al. teach



which is the same as compound I-11 of claim 101.

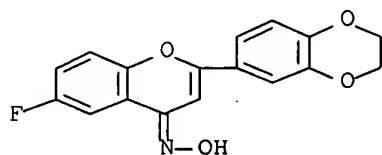
Basinski et al (Polish Journal of Chemistry (1991), 65(9-10), 1619-32) teach,



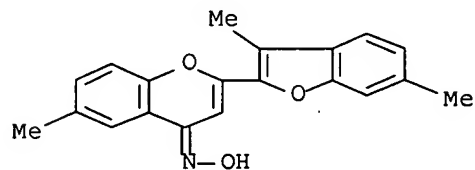
which is the same as compound I-15 of claim 101.

There are many other prior art references reading on compounds of formula I. The following are examples of prior art references not relied upon:

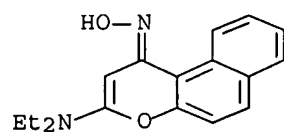
Ishchenko et al. Khimiya Geterotsiklicheskikh Soedinenii (1995), (3), 322-4.



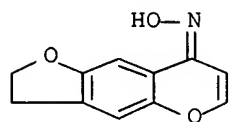
Grishko et al. *Ukrainskii Khimicheskii Zhurnal* (Russian Edition) (1985), 51(2), 211-17



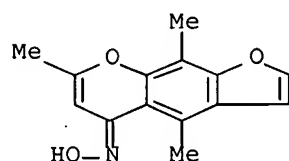
Balbi et al. *Farmaco, Edizione Scientifica* (1982), 37(6), 387-97



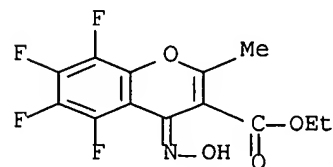
Peglion et al. US 5593989



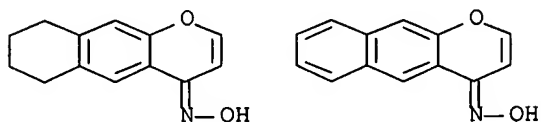
Beugelmans et al. *Tetrahedron Letters* (1976), (25), 2145-8



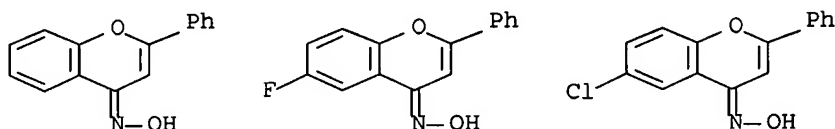
Vorozhtsov et al *Doklady Akademii Nauk SSSR* (1965), 164(5), 1046-9



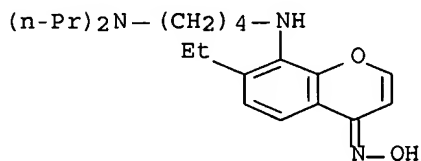
Bell et al. Australian Journal of Chemistry (1963), 16(4), 690-4



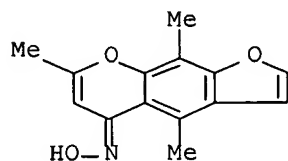
Meshcheryakova et al. Khimiko-Farmatsevticheskii Zhurnal (1976), 10(3), 37-41.



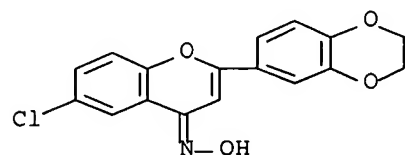
Blicke et al. Journal of Organic Chemistry (1960), 25, 693-8



Beugelmans et al. Tetrahedron Letters, 1976 25, 2145-8.



Aitmambetov et. al. (Natural Compounds (Translation of Khimiya Prirodnikh Soedinenii) (2000), 36(1), 47-50)



No Claim is allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Nizal S. Chandrakumar



D. MARGARET SEAMAN
PRIMARY EXAMINER